

Diabetic Neuropathy

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Neuromuscular fellowship

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Agenda

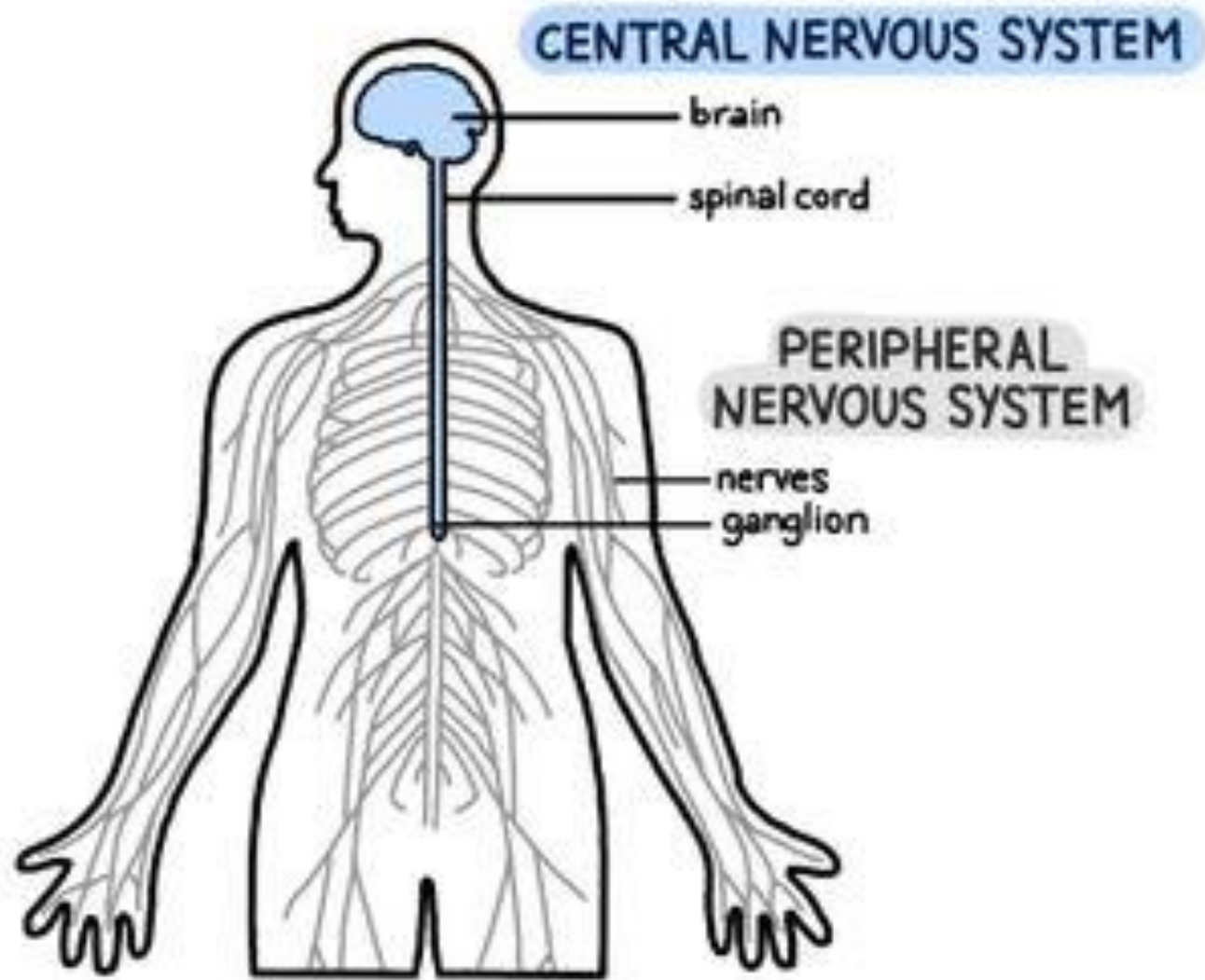
1. Definition
2. Pathophysiology
3. Epidemiology
4. Clinical Features
5. Conclusion

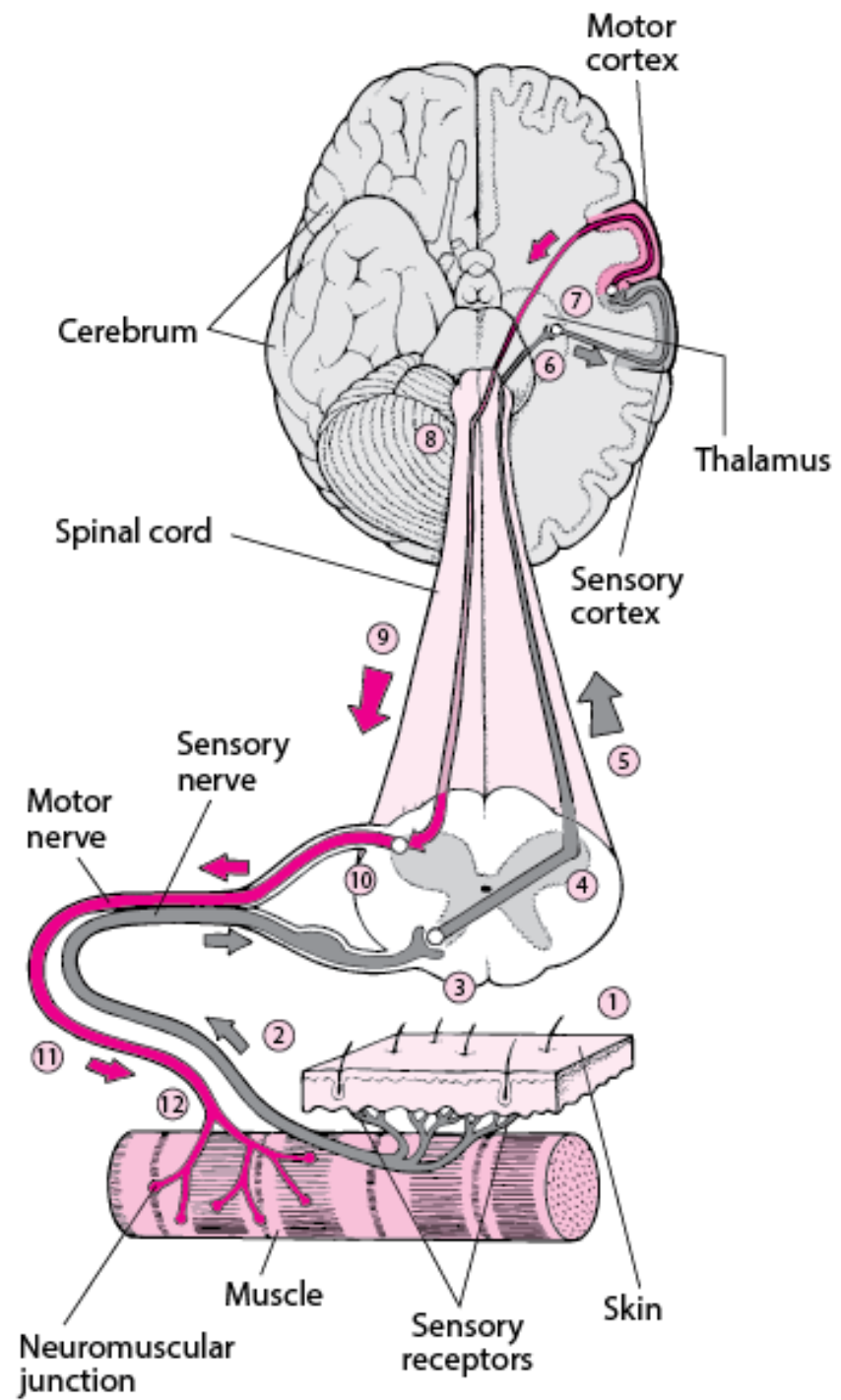




Definition







Posterior primary ramus
(to back of neck and trunk)



Root

Spinal cord

Anterior primary ramus
(to limbs; anterior and lateral trunk)

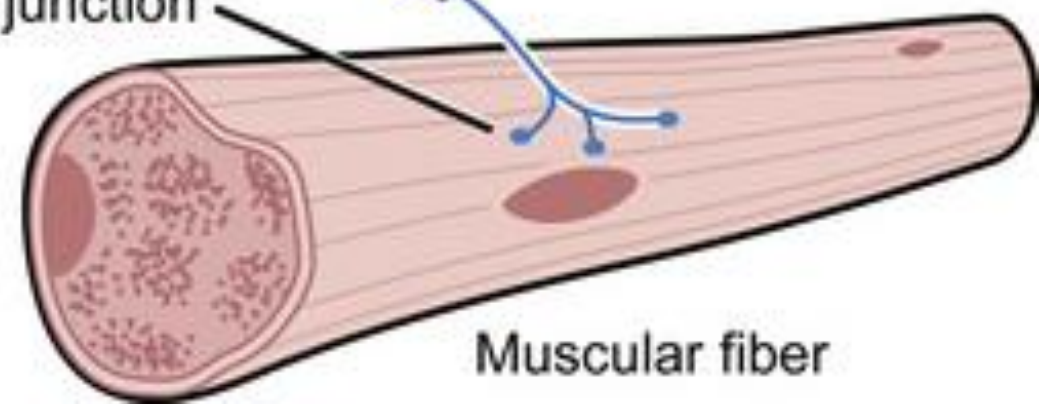


Plexus

Peripheral nerve

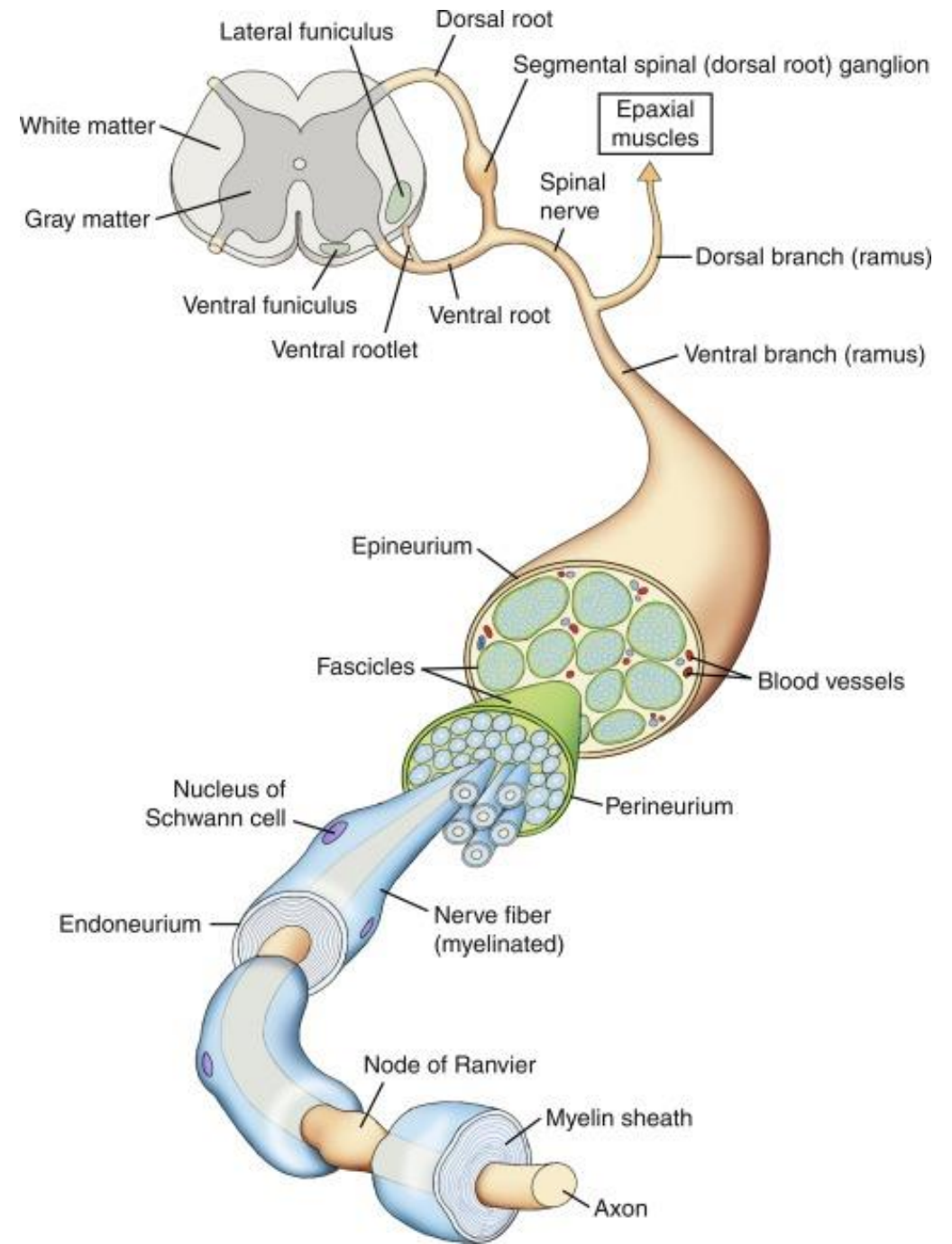
— Motor
— Sensory

Neuromuscular junction



Muscular fiber

- The peripheral nerve is a cable-like structure containing bundles of both **unmyelinated** and **myelinated** fibers and their supporting elements.



Peripheral nerve disorders

- Peripheral nerve disorders are common neurological problems caused by dysfunction of peripheral **motor**, **sensory**, or **autonomic** nerves.
- The **causes** of neuropathies are **disparate** and their **clinical** presentations highly **variable**.
- The main causes of neuropathy are **entrapment**, **systemic** diseases (**DM**), inflammatory and **autoimmune** disorders, **inherited** disorders, **ischemic** settings, **paraneoplastic** conditions, **deficiency** states, **infections**, and **toxins**.
- A logical systematic diagnostic approach to peripheral neuropathies consists of a **detailed history**, comprehensive physical and neurological **examinations**, detailed electrodiagnostic (**EDX**) studies, and possibly additional **ancillary** testing (such as autonomic testing, skin biopsy and nerve biopsy).



Diabetic neuropathy

- Diabetic neuropathy is **defined as** the presence of symptoms and signs of peripheral nerve dysfunction in individuals with diabetes after the **exclusion of** other causes (vitamin B12 deficiency and endocrine neuropathies).
- In general, the diagnosis of a **definite** diabetic neuropathy should be based on **clinical symptoms**, **objective** neurological signs, and **EDX** confirmation.
- Diabetic neuropathies result in significant **physical** and **psychological morbidity**, including disabling pain, depression, and worse quality of life, as well as increased **medical costs**.





PATHOPHYSIOLOGY OF DIABETIC NEUROPATHY



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- The etiology is most likely multifactorial.
 - Derangements of normal **metabolic** homeostasis.
 - **Autoimmunity**.
 - **Microvascular** insufficiency.



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- Neuropathy related to **type 1** diabetes is directly linked to **glycemic control**.
 - Optimal glycemic control in type 1 diabetes reduces the relative risk of neuropathy development **by 78%** and improve EDX and vibratory threshold testing results among individuals with existing DN.
 - In contrast, although still an important risk factor, hyperglycemia is much **less important** in the pathogenesis of neuropathy in **type 2** diabetes.
 - In type 2 diabetes, intensive glycemic control only reduces the risk of neuropathy by **5% to 9%**.
 - Increasing evidence indicates that individual components of the **metabolic syndrome**, including **hypertriglyceridemia**, **hypertension**, abdominal **obesity**, low levels of **high-density lipoproteins**, and **tobacco** use, are important determinants of neuropathy risk and progression in type 2 diabetes.





Epidemiology



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- **Both** type 1 and type 2 diabetes carry a high risk of neuropathy development.
 - The **prevalence** of neuropathy in the population of individuals with diabetes is **similar** between those with type 1 and type 2 diabetes, ranging from **10% to 50%**.
 - The **risk of developing symptomatic** neuropathy in patients without neuropathic symptoms or signs at the time of initial diagnosis of diabetes is estimated to be **4% to 10%** by **5 years** and **up to 50%** by **25 years**.



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- In a population cohort of diabetic patients, **two-thirds** of diabetics had **objective** evidence of some type of neuropathy, but only about **15%** had **symptomatic** degrees of polyneuropathy.
 - **Electrophysiological** studies demonstrate **subclinical** conduction abnormalities in **most** patients with IDDM after 5 to 10 years of diabetes.



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- Several recent studies have shown that patients presenting with a chronic “**idiopathic**” **axonal polyneuropathy** have nearly a **twofold** higher frequency of **undiagnosed** diabetes mellitus and impaired fasting blood glucose than age-matched controls.
 - These studies suggest that an axonal neuropathy may be the **presenting** or the earliest manifestation in diabetes.





Clinical Features



BOX 107.14 Classification of Diabetic Neuropathies

GENERALIZED SYMMETRICAL POLYNEUROPATHIES

Distal sensory or sensorimotor polyneuropathy

Small-fiber neuropathy

Autonomic neuropathy

Large-fiber sensory neuropathy

FOCAL AND ASYMMETRICAL NEUROPATHIES

Cranial neuropathy (single or multiple)

Truncal neuropathy (thoracic radiculopathy)

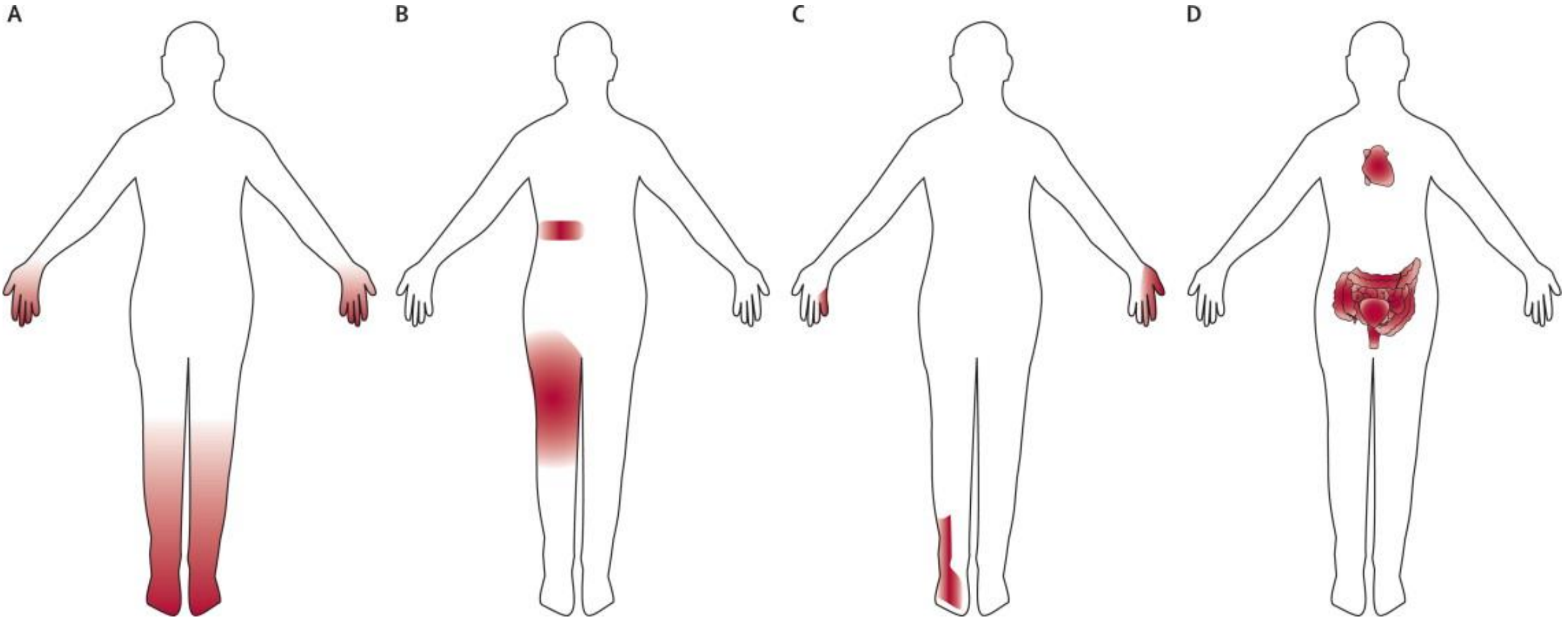
Limb mononeuropathy (single or multiple)

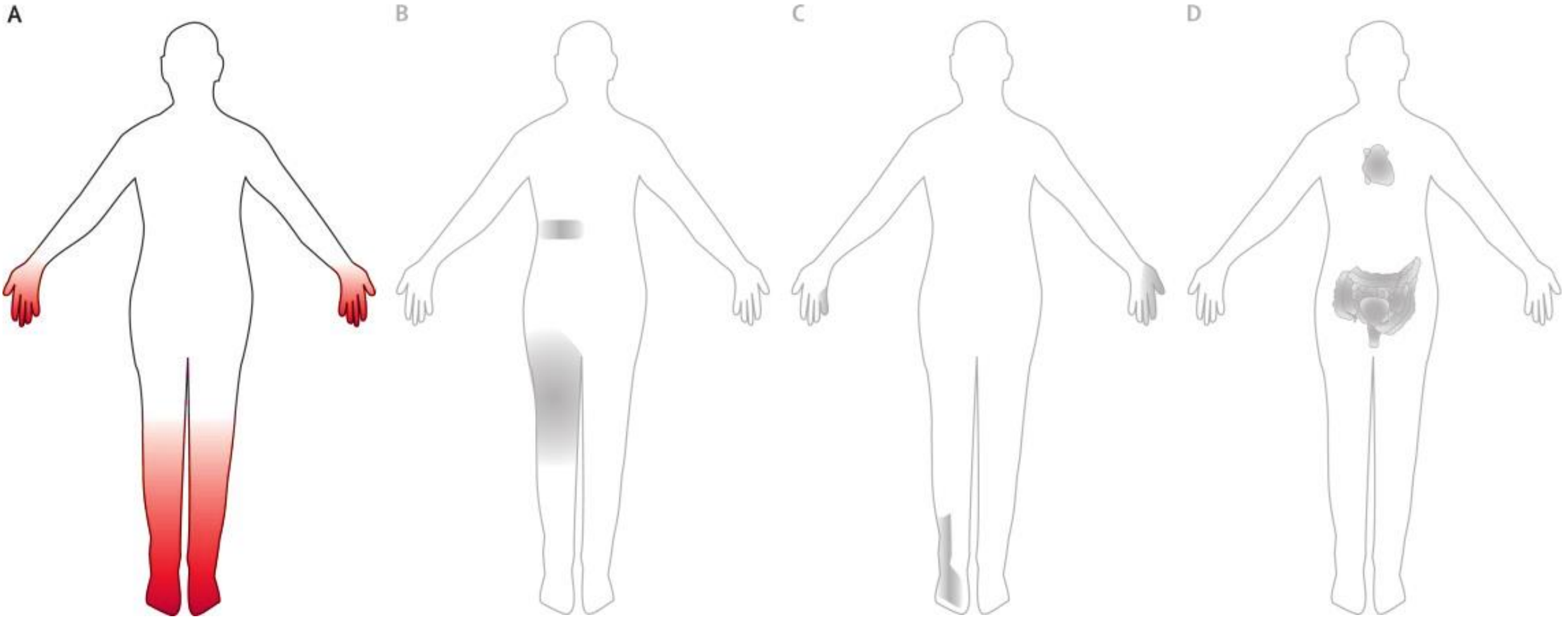
Lumbosacral radiculoplexopathy (amyotrophy, proximal neuropathy)

COMBINATIONS

Polyradiculoneuropathy

Diabetic neuropathic cachexia





Distal symmetric polyneuropathy

- The **most common** clinical presentation of neuropathy in diabetes.
- Accounting for roughly 50% **to 75%** of cases of diabetic neuropathy.
- Risk factors: disease **duration**, disease **severity**, **comorbid** medical conditions (in particular metabolic syndrome) and patient **age**.
- DSPN may be subclassified further into two major subgroups, depending on the nerve fiber type most involved: **large-fiber** and **small-fiber** variants.
- Diabetic sensory neuropathy frequently forms a continuous spectrum ranging between these two polar types.



Small-fiber neuropathy

- Early DSPN in **type 2 diabetes** (or even **prediabetes**) preferentially involves small **unmyelinated** axons, frequently causing neuropathic pain, and gradually progresses to more involvement of large myelinated axons over time.
- **Pain** of a deep, burning, stinging, aching character, often associated with spontaneous shooting pains and allodynia to light touch.
- Pain and temperature modalities are impaired, with relative preservation of vibration and joint position sensation and muscle stretch reflexes.
- The small-fiber variant is often accompanied by **autonomic** neuropathy.



Large-fiber neuropathy

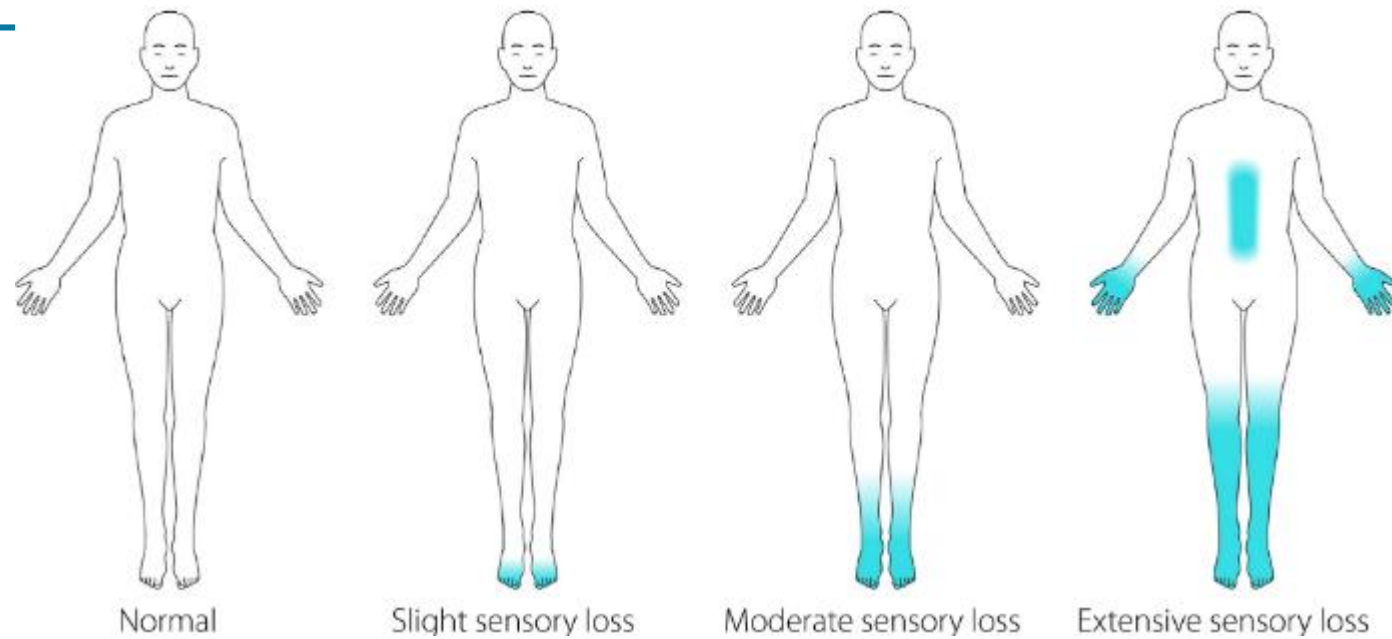
- Large-fiber involvement is **often asymptomatic**, but sensory deficit **may** be detected by careful **examination**.
- The large-fiber neuropathy variant presents with painless **paresthesia** beginning at the toes and feet, impairment of vibration and joint position sense, and diminished muscle stretch reflexes.
- In advanced cases, significant **ataxia** may develop secondary to sensory deafferentation.



Distal Symmetrical Polyneuropathy

- **Sensory** deficits predominate.
- Sensory disturbances have a **stocking-glove** distribution following a length-dependent pattern.
- Most patients will develop only a **minor motor** involvement affecting the distal muscles of the lower extremities.
- Autonomic symptoms usually correlate with the severity of the neuropathy.
- Patients with **neuropathic pain** in the setting of DSPN typically present **much earlier** in the disease course than those without pain.





- Early sensory manifestations begin in the toes, gradually spreading proximally;
- When these reach above knee level, the fingers and hands become affected.
- In more advanced cases, sensation becomes impaired over the anterior chest and abdomen, producing a truncal wedge-shaped area of sensory loss.



Diagnosis

- The diagnosis of DSPN in diabetes is based on **history**, clinical **examination** findings, and **nerve conduction studies** in select cases.
- The appropriate clinical evaluation for DSPN includes, but is not limited to, examination of muscle **strength**, deep tendon **reflexes**, and **sensation** (vibration, proprioception, thermal, pain, and light touch sensation).
- The presence of atypical features such as significant **asymmetry**, an **acute onset**, or **early motor** involvement suggests a different neuropathy type or diagnosis and should prompt further diagnostic evaluation, including nerve conduction studies and EMG.
- Although DSPN is generally symmetric (by definition), symptoms **may initially** be reported in **one limb** and then gradually evolve into a symmetric pattern over time.



Pressure perception

- 10-gram monofilament
- Those unable to detect 7 of 10 applications (at one or more sites) are at significantly elevated **risk** for painless **injury** and should be referred for appropriate podiatric foot care.



Management

- **No** disease-modifying therapies.
- To improve **glycemic control**.
- **Education** about the underlying problem.
- **Pain** management.
 - 1) **Gabapentinoids**: Gabapentin-Pregabalin
 - 2) **SNRIs**: Duloxetine-Venlafaxine
 - 3) **TCA**s: Amitriptyline
 - 4) **Sodium channel blockers**: Oxcarbazepine-Lamotrigine
 - 5) Also, **Topical** medications: Capsaicin
- **Opioids** (Tramadol) are **not** recommended.



Management

- Treatment of **modifiable risk factors**.
 - 1) To more aggressively manage **lipids** and **blood pressure**.
 - 2) To counsel on **tobacco** cessation.
 - 3) **Weight loss** through dietary modification.
- Advocating for an increase in **exercise**.
- Should be counseled on **foot care**.
 - 1) Should always wear **hard-soled shoes**.
 - 2) Should make sure to **check** their feet at least **once daily**.
 - 3) Should have a very low threshold for seeking medical attention in the setting of a **foot injury**.



Neuropathy associated with metabolic syndrome and prediabetes

- Prediabetes (impaired fasting glucose or impaired glucose tolerance) may precede the diagnosis of type 2 diabetes by **several years**.
- A hemoglobin A1c level of **5.7% to 6.4%**.
- The prevalence of neuropathy in prediabetes is approximately **10%**.
- Symptoms, EDX abnormalities, and intraepidermal nerve fiber density reduction consistent with a predominantly **small-fiber** neuropathy that may be either **painful or painless**.
- Changes are less pronounced than in their diabetic counterparts.



Impaired glucose tolerance neuropathy

- A smaller number of patients may present with **autonomic** dysfunction, primarily manifesting as reduced cardiovagal function with a resting tachycardia and reduced exercise tolerance.
- Among individuals with otherwise “idiopathic” neuropathy, the presence of prediabetes is approximately **25%**.
- The implication for clinical practice is that patients with **undiagnosed** painful peripheral neuropathy **should** undergo **OGTT**.
- Early diagnosis followed by improved lifestyle may result in **reversal** of impaired glucose tolerance and neuropathy.



Treatment-Induced Neuropathy of Diabetes

- Previously known as insulin neuritis, or acute painful neuropathy.
- Develops **suddenly following rapid improvement** in glycemic control in the setting of **chronic hyperglycemia**.
- Most commonly seen after a significant treatment change in individuals with type 1 diabetes who have had chronic hyperglycemia or in individuals with newly discovered type 2 diabetes with an unknown period of hyperglycemia combined with an aggressive lowering of the hemoglobin A1c.
- The neuropathy predominantly involves **small fiber** sensory and autonomic nerve fibers.
- Characterized by the **acute** onset of neuropathic **severe burning pain** in a **length-dependent** or generalized distribution, often with accompanying **autonomic** symptoms.

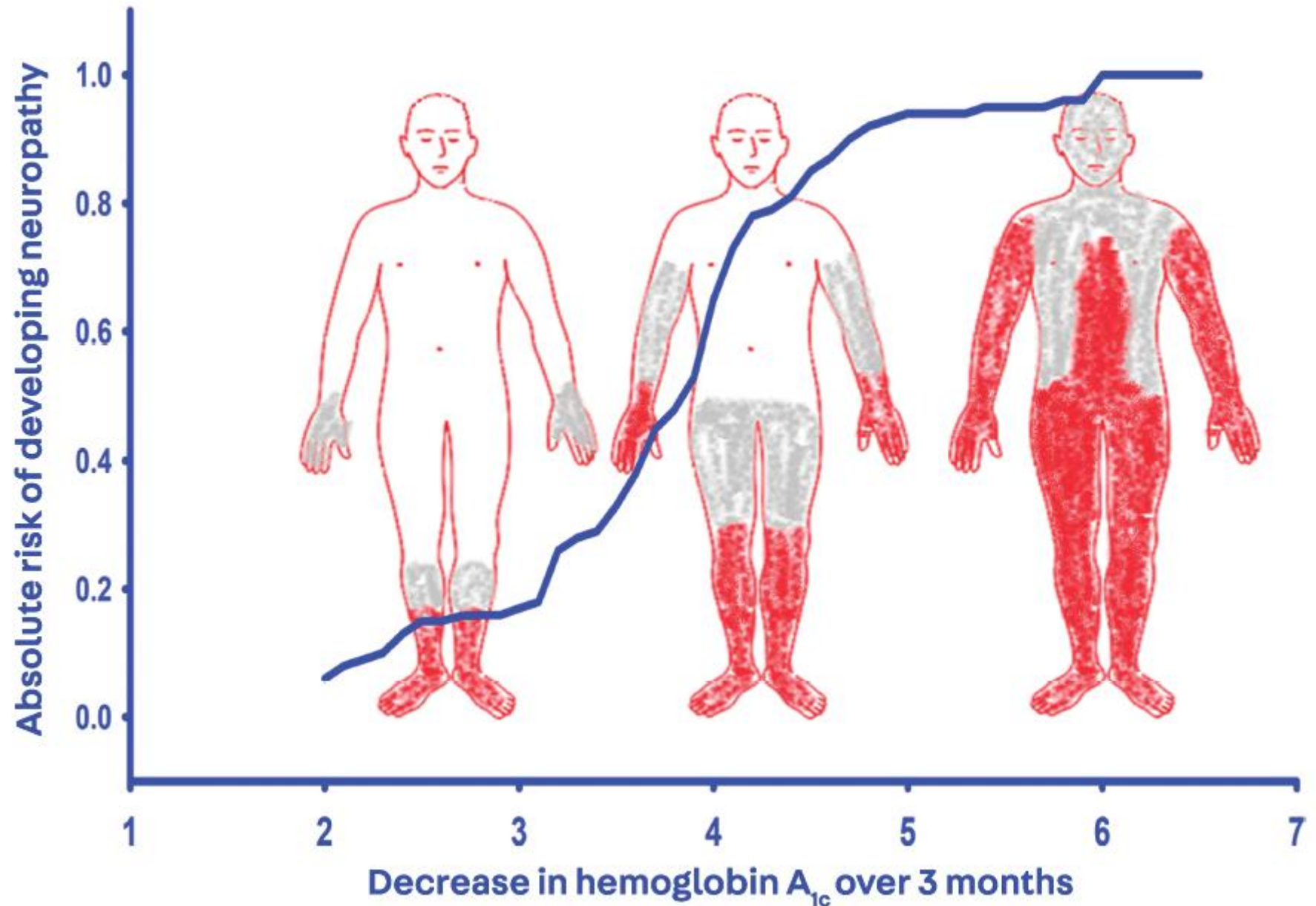


Treatment-Induced Neuropathy of Diabetes

- Symptoms typically begin **2 to 8 weeks** after the change in glucose control.
- Pain persists for **weeks** or up to several **months**, with spontaneous resolution to follow.
- **Autonomic** symptoms are sometimes prominent, including orthostatic intolerance or hypotension, hyperhidrosis or anhidrosis, early satiety, and erectile dysfunction, but they are **frequently overlooked** given the severity of the neuropathic pain.
- The severity of neuropathy in treatment-induced neuropathy of diabetes is tied to the **magnitude** and **rate** of the change in hemoglobin A1c.



- Individuals with the **largest changes** in glucose control have the **largest region** of body involvement, the **most severe** pain, and the greatest symptoms of **autonomic** dysfunction.



Treatment-Induced Neuropathy of Diabetes

- In addition to the development of neuropathy, individuals who develop treatment-induced neuropathy of diabetes also frequently have renal and retinal involvement simultaneously.
- The majority of individuals with treatment-induced neuropathy of diabetes have significant progression of proliferative retinopathy over a period of 12 months.
- Renal function may decline, although increased microalbuminuria is the most common manifestation.



Management

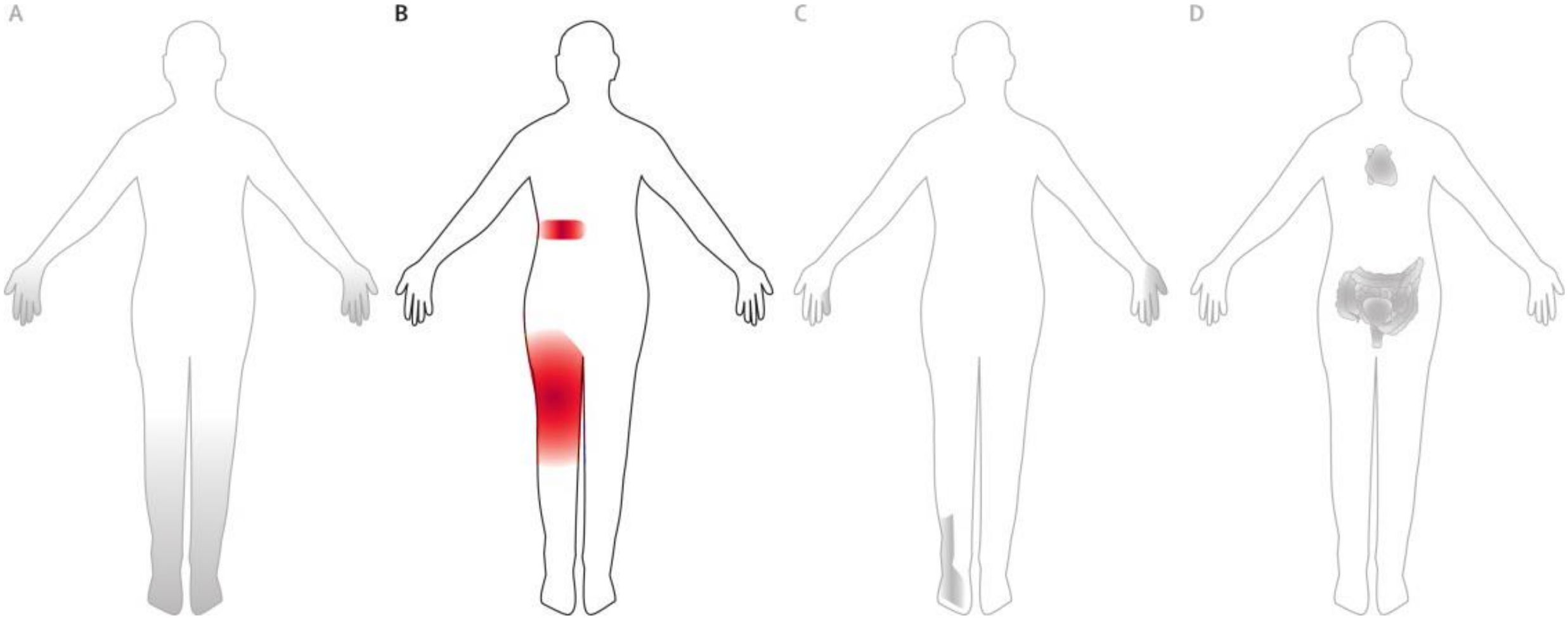
- Focused on preventing neuropathy **progression**, managing **symptoms** and preventing **recurrence**.
- 1. Often improve with stable glucose control => Encouraging glucose **stabilization** at the **current** hemoglobin A1c level until symptoms begin to improve.
- 2. **Two** and even **three** agents may be necessary for pain control (TCAs should be used cautiously as they may worsen orthostatic symptoms).
- 3. Avoiding dramatic improvements in hemoglobin A1c levels in individuals with chronic hyperglycemia is recommended (limiting change to **1%** reduction in the hemoglobin A1c **per month**).



Diabetic neuropathic cachexia

- An **acute** and severe **painful** diabetic neuropathy associated with precipitous severe **weight loss**, depression, insomnia, and impotence in men.
- The syndrome is more common in **men** with **poor glucose control**.
- Improved glucose control and weight gain often result in recovery and improvement of EDX abnormalities.
- The reason for profound weight loss, severe pain, and spontaneous recovery remains obscure.





Diabetic Lumbosacral Radiculoplexus Neuropathy

- Different presentations of the same basic involvement of multiple nerve roots or proximal nerve segments. : **Diabetic amyotrophy**, thoracolumbar radiculopathy, and proximal or diffuse lower extremity weakness.
- The incidence: approximately 4.2 per 100,000 per year.
- **Most common** in middle-aged (older than **50 years**) patients with **type 2** diabetes.
- Is more common in **men** than in women.
- The disorder is **rare** in **young** adults or **children**.
- The onset is **unrelated** to the **duration** of diabetes, and **often** have fairly **well-controlled** diabetes.
- Pathologic data suggest it is caused by a **microvasculitis** resulting in **ischemic** nerve injury.



Diabetic Lumbosacral Radiculoplexus Neuropathy

- Typically, **unilateral** severe **pain** in the **lower back**, **hip**, and **anterior thigh** heralds the onset of neuropathy.
- Within **days to weeks** **asymmetrical weakness** ensues, affecting **proximal** and, to a **lesser** extent, **distal** lower-extremity muscles (iliopsoas, gluteus, thigh adductor, quadriceps, hamstring, and anterior tibialis).
- **Less** commonly, patients may present with a **symmetric** motor-only form.
- Reduction or absence of knee and ankle jerks is the rule. Numbness or paresthesias are **minor** complaints.
- **Weight loss** occurs in **more than half** of patients.



Diabetic Lumbosacral Radiculoplexus Neuropathy

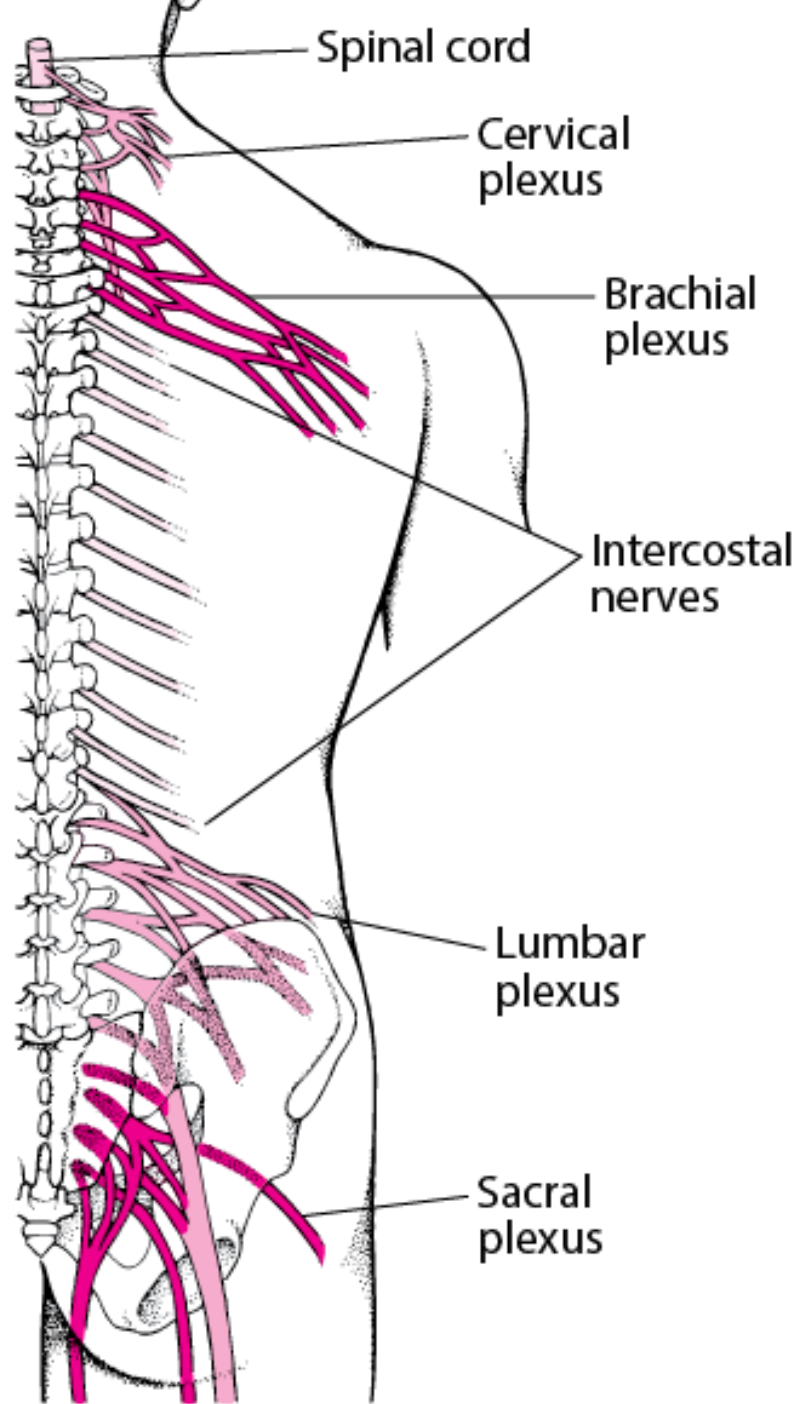
- The progression may be **steady or stepwise** and may continue for many **months** (in some cases as long as **18 months**).
- **Pain** usually **recedes** spontaneously **long before** motor strength begins to improve.
- **Recovery** takes **up to 24 months** because of the slow rate of axonal regeneration.
- In **many** cases, **mild to moderate** weakness persists indefinitely.
- In some cases, the **opposite** leg becomes affected **after** a latency.
- Most patients require assistance with ambulation and aggressive pain management.



Management

- There are currently **no effective** disease-modifying treatments.
- The management is focused on **pain management** and adaptive **devices** to improve quality of life.
- Although a beneficial effect of **immunomodulating** therapies has been proposed, controlled studies have shown **no** positive effect for corticosteroids in enhancing the recovery of the **motor** deficit.
- A small randomized trial suggested that **IV methylprednisolone** **may** help neuropathic **refractory pain** associated with diabetic lumbosacral radiculoplexus neuropathy.





Diabetic Truncal Neuropathy (thoracic radiculopathy)

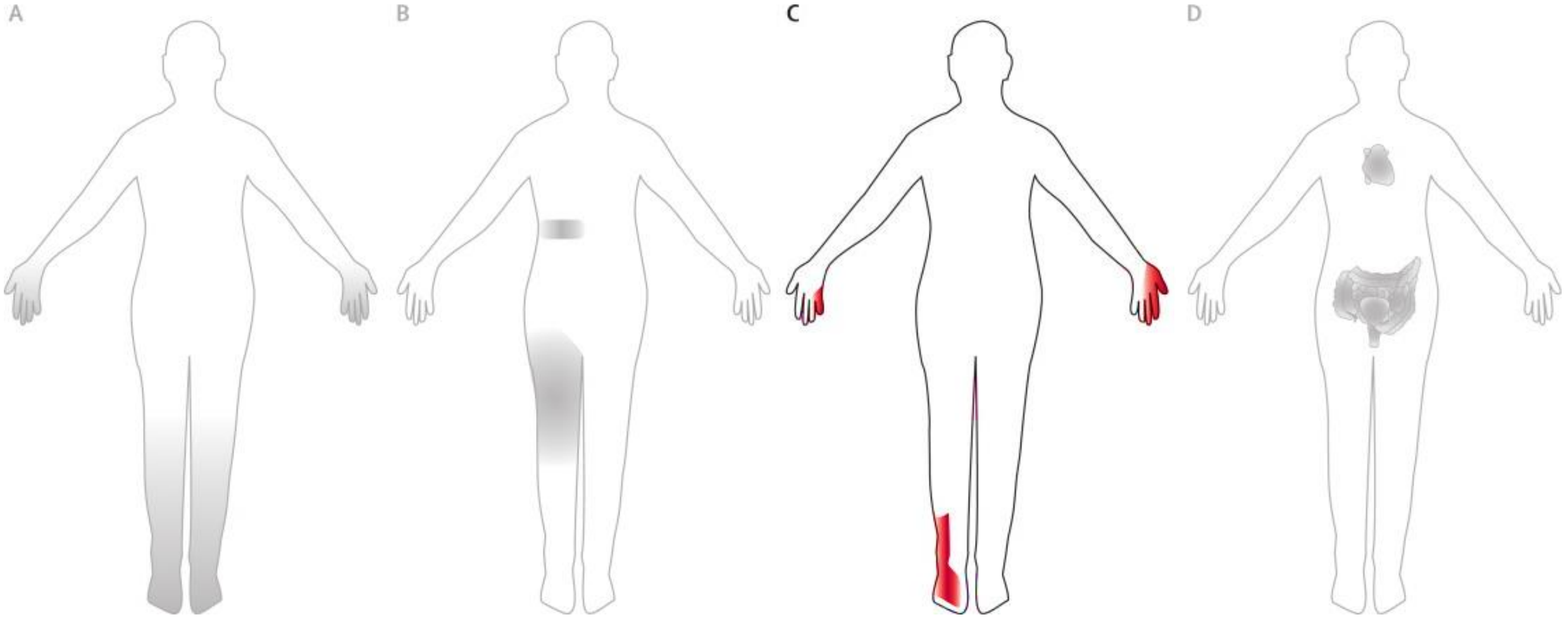
- Involving the T4 through T12 spinal nerve roots causes pain or dysesthesias in areas of the chest or abdomen, thereby producing diagnostic confusion.
- **Bulging** of the abdominal wall as a result of weakness of abdominal muscles may also occur.



Diabetic Truncal Neuropathy (thoracic radiculopathy)

- This unique truncal pain is seen in **older** patients with **NIDDM**.
- May occur either in isolation or together with the typical lumbosacral radiculoplexopathy.
- Patients describe burning, stabbing, boring, beltlike pain and contact with clothing can be very unpleasant.
- The onset may be either **abrupt or gradual**.
- In some patients preceded or accompanied by a profound **weight loss**.
- The symptoms may **persist** for several **months** before gradual and spontaneous resolution within **4 to 6 months**.





Limb Mononeuropathy

- Caused by two basic mechanisms: nerve **infarction** or **entrapment**.
- Mononeuropathy secondary to nerve **infarction** has a stereotyped presentation, with **abrupt** onset of **pain followed by** variable **weakness** and atrophy.
- Mononeuropathies due to nerve **entrapment** are **more common** than nerve infarctions.
- Entrapment neuropathies, including median mononeuropathy at the wrist (carpal tunnel syndrome), ulnar mononeuropathy at the elbow (cubital tunnel syndrome), and fibular (peroneal) mononeuropathy at the fibular head are more prevalent in individuals with diabetes when compared to the general population.



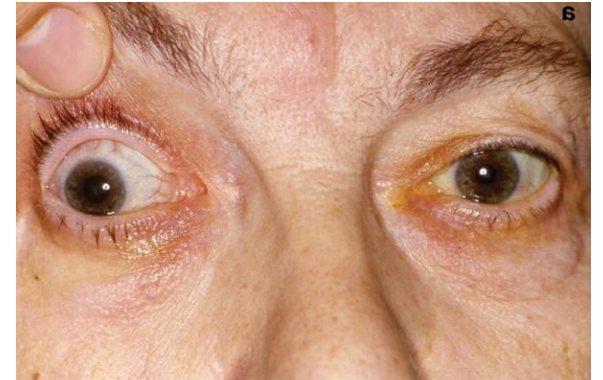
Limb Mononeuropathy

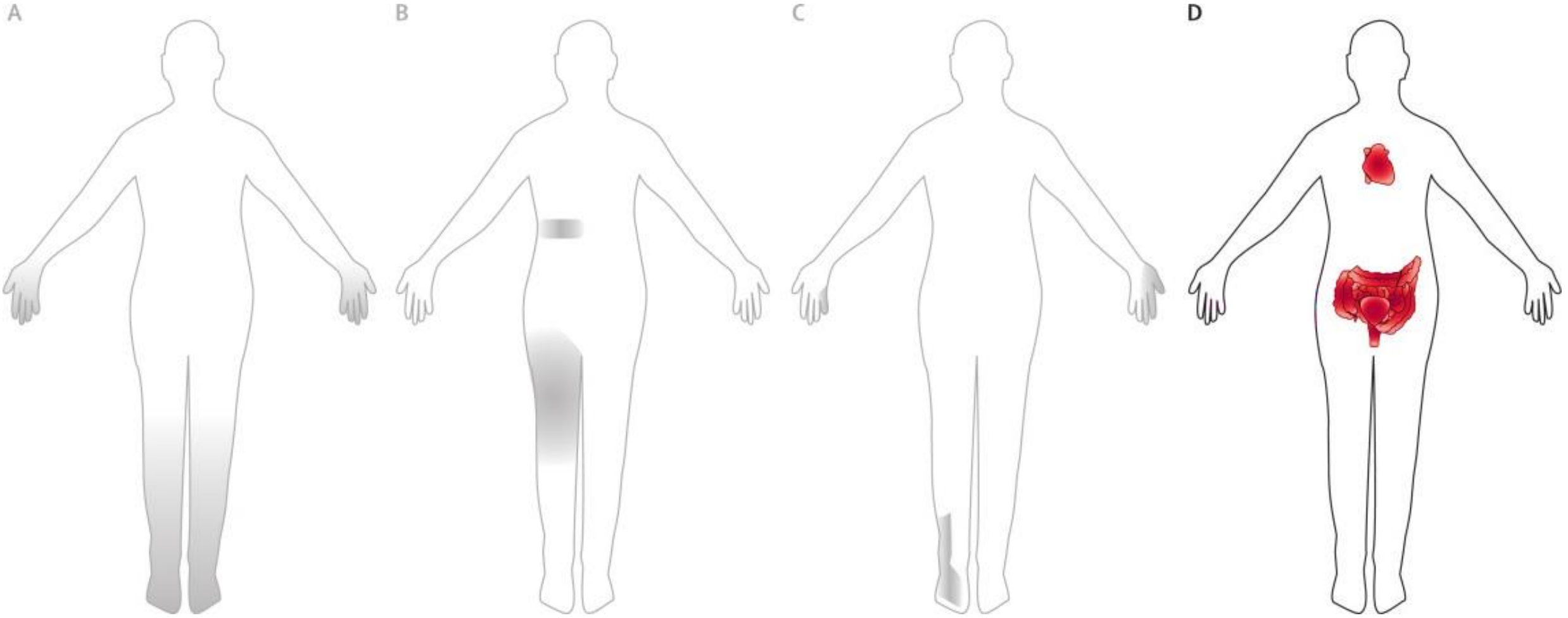
- Diabetes mellitus is a risk factor for single or multiple entrapment neuropathies.
- Diabetes is found in 8% to 12% of patients presenting with CTS.
- The risk for CTS is more than twofold for patients with diabetes than in the general population.



Cranial Mononeuropathies

- A **third**-nerve palsy is the most commonly encountered diabetic cranial mononeuropathy.
- **Pupillary sparing**, the hallmark of diabetic third-nerve palsy, results from ischemic infarction of the centrifascicular oculomotor axons due to diabetic vasculopathy of the vasa nervorum.
- With decreasing frequency, the **fourth**, **sixth**, and **seventh** nerves are also affected.





Autonomic Neuropathy

- In one study, autonomic impairment was present in **54%** of IDDM and **73%** of NIDDM.
- **Diverse** spectrum of clinical manifestations because of the **different** organ systems involved.
- Usually **correlates with** the severity of **somatic** neuropathy.
- The spectrum of autonomic involvement ranges from **subclinical** functional impairment of cardiovascular reflexes and sudomotor function to **severe** cardiovascular, gastrointestinal, or genitourinary autonomic dysfunction.
- Patients **may not** notice the symptoms of cardiovascular autonomic neuropathy for **several years**, and late diagnosis increases the risk of mortality.



Diabetic Cardiovascular Autonomic Neuropathy

- **Prolonged hyperglycemia** is the primary risk factor.
- Decreased **heart rate variability** has also been reported in up to **38%** of individuals with **prediabetes**.
- Among individuals with NIDDM, **traditional** cardiovascular risk factors (hypertension, dyslipidemia) are also associated with DCAN.
- DCAN is associated with a significant increase in both **morbidity** and **mortality** (cardiovascular events, including arrhythmia and MI).
- The American Diabetes Association recommends **screening all** patients with existing **microvascular** complication of diabetes (ie, DSPN, retinopathy, or nephropathy) for signs and symptoms of DCAN.



Diabetic Cardiovascular Autonomic Neuropathy

- **Early** signs are from **parasympathetic** dysfunction of vagal nerve and include **elevated resting heart rate** and impaired **heart rate variability** which are often **asymptomatic**.
- As cardiovascular autonomic neuropathy becomes more severe, **orthostatic hypotension** (defined as a fall in blood pressure of >20mmHg systolic and >10 mm Hg diastolic when going from lying to sitting or sitting to standing after 3 minutes) develops, which is **the most severe** and debilitating form of cardiovascular autonomic neuropathy.
- Patients with diabetes who have orthostatic hypotension in the setting of cardiovascular autonomic neuropathy have a **5- to 10-year mortality** range between **27% and 56%**.



Diabetic Cardiovascular Autonomic Neuropathy

- At present, **no** treatment exists for the underlying disease.
- As a consequence, the primary goal is **prevention** of disease **development** and **progression** with glycemic control and aggressive management of other features of metabolic syndrome.
- Among patients with orthostatic hypotension, **symptomatic** management should also be considered.



Nonpharmacologic Interventions for Orthostatic Hypotension

In conjunction with a patient's primary care provider, review the existing medication list and discontinue medications that may be contributing to hypotension; offending agents may include antihypertensive medications, antidepressants, and dopaminergic medications for Parkinson disease

Increase intravascular volume

- ◆ Increase fluid intake (up to 1.5-3 L/d)
- ◆ Liberalize salt intake (up to 6-10 g/d of sodium)
- ◆ Waist-high compression stockings to reduce vascular pooling, increase venous return, and increase blood pressure (at least 15-20 mm Hg pressure), although the effect may be limited because of pooling in the splanchnic vasculature

Modify behavior

- ◆ Arise slowly, particularly in the morning when orthostatic tolerance is the lowest
- ◆ Elevate the head of the bed 30 to 45 degrees to avoid supine hypertension and nocturnal diuresis
- ◆ Avoid triggers: eg, Valsalva-like maneuvers, overheating, large carbohydrate-rich meals
- ◆ Continue a modified exercise regimen since deconditioning can worsen orthostatic hypotension; focus on recumbent activities

TABLE 5-2

Pharmacologic Interventions for Orthostatic Hypotension

Medication and mechanism of action	Dosing	Potential adverse effects
Fludrocortisone Synthetic mineralocorticoid, expands volume by increasing sodium and water reabsorption	0.1-0.2 mg/d administered as 1 or 2 doses; start with 0.05 mg/d	Hypokalemia, supine hypertension, peripheral edema, renal failure; use cautiously in patients with congestive failure
Midodrine Direct α_1 -adrenergic receptor agonist	2.5-10 mg 3 times a day administered every 3-4 hours during daytime hours	Severe supine hypertension, piloerection, urinary retention; do not use within 4 hours of bedtime; use cautiously in patients with congestive heart failure and chronic renal failure
Droxidopa Synthetic norepinephrine precursor	100-600 mg, 3 times a day, the last dose needs to be administered at least 3 hours before sleep	Headache, supine hypertension, nausea, fatigue; use cautiously in patients with congestive heart failure and chronic renal failure
Pyridostigmine Acetylcholinesterase inhibitor	Start with a 30-mg test dose; if well tolerated, increase to 60 mg, can be administered up to 3 times daily; rarely use more than 120 mg per dose	Wheezing, abdominal pain, diarrhea, hyperhidrosis

Gastroparesis

- Causes delayed transit of food (solids or liquids) from the stomach into the small intestine.
- It is present in **up to 50%** of individuals with diabetes.
- Many patients report postprandial fullness, nausea, bloating, or vomiting, although some patients may be asymptomatic.
- It further **complicates glycemic control** by causing a mismatch between glucose absorption and administration of insulin.
- Objective assessment of gastroparesis severity is recommended.
- A separate and potentially reversible component is directly related to hyperglycemia.



Treatments

- Having patients eat **smaller, more frequent** meals. (this strategy can further complicate glycemic control)
- Avoiding dietary **fiber** and **fat** is recommended.
- Removal of any offending **medications** (such as opioids, clonidine, tricyclic antidepressants, calcium channel blockers, dopamine agonists, muscarinic cholinergic receptor antagonists, glucagonlike peptide 1 [GLP-1] agonists, phenothiazines, and cyclosporine)
- **Metoclopramide** (duration of therapy **beyond 5 days** is **not** recommended)



Constipation

- Up to **60%** of patients affected.
- Constipation due to colonic hypomotility is more common than diarrhea.
- The patient's **medication** list should be closely investigated.
- Treatment:
 1. Food and dietary change (eating **fiber-rich** foods)
 2. More **exercise**
 3. Bulking agents such as **psyllium**
 4. Osmotic laxatives such as **lactulose**



Diarrhea

- It is typically a **profuse** and **watery** diarrhea that usually presents **during sleep**.
- It is more common in individuals with **type 1** diabetes.
- Often associated with fecal **incontinence**.
- Associated weight loss or malabsorption is **rare**.
- Reported in up to **20%** of individuals with diabetes.
- It may alternate with constipation or may persist as diarrhea for hours at a time.
- Loperamide, codeine, combination diphenoxylate and atropine, or tincture of opium.



Bladder Dysfunction

- Reported in up to **50%** of individuals with diabetes.
- The symptoms of urinary autonomic dysfunction develop **insidiously** and **progress slowly**.
- One of the initial symptoms of autonomic neuropathy involving the bladder is **impaired sensation of fullness**.
- As neuropathy severity increases, bladder atony leads to prolonged intervals between voiding, gradually increasing **urinary retention**, and finally **overflow incontinence**.
- Encouraged to void routinely **every few hours** to prevent urinary retention (or **bethanechol**).
- **Medications** that impair detrusor activity include anticholinergic agents, tricyclic antidepressants, and calcium channel antagonists.



Sexual Dysfunction

- Diabetic neuropathy leads to dysfunction of vaginal exocrine glands, resulting in dryness and tissue irritation, further compounding **painful intercourse**; with the frequency of **70%** in women with type 2 diabetes.
- **Erectile dysfunction** is highly prevalent in men with diabetes, noted in up to **75%** of male patients; the underlying pathophysiology is a combination of vascular, neurologic, and psychological factors.
- The other complication is **retrograde ejaculation**.
- Although a number of medications (sildenafil and vacuum-erection device) exist to treat erectile dysfunction, they become less effective as neuropathy and vascular disease worsen.



Sudomotor Function

- May present as the **earliest** clinical manifestation of neuropathy.
- Sudomotor abnormalities result in **distal anhidrosis**, typically presenting in a **stocking-and-glove** distribution.
- Interestingly, patients do not present with symptoms related to distal anhidrosis but instead report **proximal hyperhidrosis** to maintain thermoregulation.
- Patients feel that they are sweating too much over their **head** and **trunk**.
- Another classic finding in diabetic neuropathy, although less common than distal anhidrosis, is **gustatory sweating**. Sweat will appear over the face, head, neck, shoulders, and chest after eating.
- Oral or topical **glycopyrrolate** may prove partially effective in some patients.



TABLE 2-2

Impact of Medications and Other Agents on Autonomic Function

Autonomic Symptoms/Signs	Potentially Causative Agents
Orthostatic hypotension	Antidepressants, antihypertensive medications, α_1 -adrenoreceptor antagonists, antiparkinsonian dopaminergic agents
Gastroparesis	Opioids, clonidine, tricyclic antidepressants, calcium channel blockers, dopamine agonists, muscarinic cholinergic receptor antagonists, glucagonlike peptide 1 (GLP-1) agonists, phenothiazines, cyclosporine
Constipation	Calcium channel antagonists, opioids, anticholinergic medications
Diabetic diarrhea	Metformin, sorbitol-containing foods
Bladder dysfunction	Anticholinergic agents, tricyclic antidepressants, calcium channel antagonists (impair detrusor activity); α_1 -adrenoreceptor agonists (increase urethral sphincter tone), α_1 -adrenoreceptor antagonists (decrease urethral sphincter tone)
Sexual dysfunction	Antidepressants, antihypertensive medications, statins, antihistamines



Conclusion



Conclusion

- Unfortunately, once the diabetic neuropathy is established, the existing damage is largely **irreversible**.
- The cornerstone in the treatment of diabetes and its complications is **prevention** of disease **development** and **progression** with **glycemic control** and aggressive management of other features of **metabolic** syndrome, and **symptom** management including pain treatment.





THANK YOU 😊